PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X-16305

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)
1 JAN 2006

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/004812	16.02.2005	01.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, A61K31/4162, C07D471/04, A61K31/437, A61K31/55, A61P35/00, A61P17/02

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9-10

because:

☒ the said international application, or the said claims Nos. 9-10 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Reference is made to the following documents:

D1: WO02/094833
D2: WO03/097639
D3: WO01/62756
D4: WO2004/050659 (P-document)

Document D1 has been published between the priority date and the filing date of the present application. According to Rule 64.3 PCT, this document may not be taken into account for the assessment of novelty and inventive step during the international phase. The attention of the applicant is however drawn to the fact that this document may prove relevant in the examination process during regional phase.

The present application deals with fused pyrazole derivatives as TGF-beta signal inhibitors for the treatment of fibrosis and neoplasms.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Document D1 describes fused pyrazole derivatives as TGF-beta signal inhibitors for the treatment of cancer, fibrosis, AD, HIV, etc. According to Formula (I) of D1, R1 may represent a pyridine ring and R2 a quinazoline substituted with a hydroxy (i.e. enol form of the ketone), an alkyl or an halogenated alkyl. Thus, Formula (I) of D1 overlaps with

the present subject-matter when these specific structural features are combined. However, such a combination is neither illustrated nor suggested in D1 and represents therefore a new teaching which provides a contribution over the prior art. Novelty of claims 1-10 is acknowledged with regard to document D1 (Art. 33(2) PCT).

Document D2 discloses benzoxazine and benzoxazinone triazole derivatives as TGF-beta signal inhibitors for the treatment of fibrosis. Examples 1-2, 4-6 and 11 of D2 describe various compounds substituted with a pyridin-2-yl- and a benzoxazin-3-one moiety. However, the compounds of D2 possess a triazole core structure and differ therefore from the present claimed subject-matter. Claims 1-10 may also be considered novel with regard to document D2 of the prior art (Art. 33(2) PCT).

Document D3 deals with 4-pyridin-2-ylimidazole derivatives as TGF-beta signal inhibitors for the treatment of osteoporosis, fibrosis, AD, etc. Example 166 of D3 reveals a compound substituted with a pyridin-2-yl- and a benzoxazin-3-one moiety. Since the compounds of D3 are based on an imidazole core structure, they differ from the present claimed subject-matter. Therefore, novelty of claims 1-10 is also established vis-à-vis document D3 of the prior art (Art. 33(2) PCT).

2. Document D1, which is considered to represent the most relevant state of the art, disclose fused pyrazole derivatives with TGF-beta signal transduction inhibitory activity. The compounds of claims 1 represent a new selection over the disclosure of D1.

The problem to be solved by the present invention may therefore be considered as the provision of further fused pyrazole derivatives useful in the treatment of TGF-β mediated diseases.

Starting from D1, it appears that all the compounds claimed therein are expected to exhibit the claimed activity as long as the characteristic core structure is present. D1 disclose the use of a quinazoline substituted with a hydroxy (i.e. enol form of the ketone) and an alkyl or an halogenated alkyl on the pyrazole moiety. Moreover, all the examples of D1 comprise a 3-pyridin-2-yl substituent on the fused pyrazole ring. Therefore, the mere selection of a specific family of compound within a broader group known for its biological activity cannot be considered inventive in the sense of Art. 33(3) PCT since

there is a clear indication for the skilled to seek in this direction. Hence, no inventive step is present in the subject-matter of claim 1.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 8-10, which therefore are also considered not inventive.

Dependent claims 2, 5-7 do not seem to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

3. Claim 3 deals with pyrazole derivative substituted with a quinoxalinone. According to document D1, the substitutent in 2-position of the pyrazole can vary greatly without modification of the physiological activity of the compounds (see definition of R2 in D1). Therefore, the skilled person would expect that the mere exchange of a quinazolinone with a quinoxalinone (i.e. modification of the positions of the carbonyl and the nitrogen atom) would also lead to active compounds. Furthermore, the same criteria should be apply to assess inventive step and the content of the application. Since the quinazolinone and quinoxalinone ring are considered alternative solutions in the application, i.e. for the skilled person, these moiety are also considered to represent an alternative solution to the quinazolinone disclosed in D1. Therefore, the subject-matter of claim 3 lacks an inventive step in the sense of Art. 33(3) PCT.

4. The same reasoning applies, mutatis mutandis, to the subject-matter of claim 4, which therefore is also considered not inventive. Moreover, the solution proposed in dependant claim 4 lies in the use of a benzoxazinone substituent. Such a substituent is not disclosed in document D1. However, this feature has already been employed for the same purpose in the compounds of D2 and D3. Since D2 and D3 deal with 5-membered nitrogen-containing heteroaryl derivatives and the fused pyrazole structure is already known from D1 for the same biological activity, it would be obvious for the person skilled in the art to apply this feature with corresponding effect to the compounds described in D1, thereby arriving at the compounds according to claim 4. Therefore, the compounds of claim 4 do not seem to imply an inventive step with regard to the combination of D1 with either D2 or D3 (Art. 33(3) PCT).

5. For the assessment of the present claims 9-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/050659	17/06/2004	24/11/2003	27/11/2002